REMARKS

Because this Amendment After Final is only cancelling claims and addressing the Examiner's arguments set forth in the Office Action dated 23 December 2008, Applicants submit that this amendment does not raise new issues.

Claim Amendments

Claims 226-234 and 246-248 have been canceled by this amendment.

Applicants submit that this amendment does not constitute new matter and its entry is requested.

Summary of the Claimed Invention

A. Amplification of Target Viral RNA Sequence and Reference RNA Sequence

In a first aspect, claims 190-225 and 242-245 are directed to **a method for the amplification of target viral RNA and a reference RNA in a sample**. In accordance with this aspect, (i) a known quantity of a reference RNA sequence is added to a sample containing a viral RNA sequence, (ii) the target viral RNA sequence and the reference RNA sequence are simultaneously amplified and (iii) the amounts of amplified products are measured. The reference RNA sequence can be used as an internal standard. The reference RNA sequence comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same or different oligonucleotides. The amplified target viral RNA sequence and the amplified reference RNA sequence can be distinguished by size or by probes. These claims **only** relate to the amplification of a target viral RNA sequence and a reference sequence.

B. Quantitation of Target Viral RNA Sequence

In a second aspect, claims 249-255 are directed to **a method for the quantitation of target viral RNA in a sample**. In accordance with this aspect, (i) a known quantity of a reference RNA sequence is added to a sample containing a viral RNA sequence, (ii) the target viral RNA sequence and the known quantity of the reference RNA sequence are simultaneously

amplified, (iii) the amounts of amplified products are measured and (iv) the relative amount of the target viral RNA present in the sample before amplification is determined from the amounts of the amplified target viral RNA sequence and the amplified reference RNA sequence. The reference RNA sequence can be used as an internal standard. The reference RNA sequence comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same or different oligonucleotides. The amplified target viral RNA sequence and the amplified reference RNA sequence can be distinguished by size or by probes. These claims **only** relate to the quantitation of the amount of viral RNA present in the sample.

Priority

The Examiner has concluded that the limitation "same oligonucleotides" does not have support in the earlier filed application Serial No. 07/148,959 ('959 application) and thus, the instant application does not get priority back to 27 January 1988. In arriving at this conclusion, the Examiner cites the paragraphs on page 3 of the '959 application preceding the paragraph at page 3 of the '959 application (i.e., page 3, lines 23-26) which Applicants had cited for support of priority in the Amendment filed 17 September 2008 and Example III of the '959 application. With respect to considering the paragraph at page 3, lines 23-26 and the preceding paragraphs, the Examiner contends that

> the reference RNA in the cited paragraph is referring to a beta actin gene, and not to the reference maxigene as asserted by the Applicants.

With respect to Example III, the Examiner contends that it discloses the "use of a separate primer for maxigene amplification. Applicants submit that the Examiner has incorrectly analyzed the specification of the '959 application and has not considered the disclosure in the '959 application as a whole.

Initially, it appears to Applicants that the Examiner appears to be confused by the use of the terms "fourth primer," "maxigene primer" and "maxigene" in the specification of the '959 application. Although the specification does mix up the use of the terms "primer" and "reference RNA" with respect to the "maxigene," Applicants submit that the remainder of the specification

of the '959 application is clear that the specified "fourth primer," "maxigene primer" and "maxigene" relate to a reference RNA sequnece. Applicants believe that the draftsman of the '959 application could have eliminated any confusion in use of the terms "fourth primer," "maxigene primer" and "maxigene" if he had been consistent in the use of the terms "fourth primer," "maxigene primer," "maxigene" and "reference RNA sequence." Nevertheless, Applicants submit that it is clear from the '959 application that each of these specified terms relate to a reference RNA sequence for a target viral RNA and not to the beta actin gene as asserted by the Examiner.

The '959 application is directed to the simultaneous amplification of a viral RNA present in a sample with at least one other RNA sequence. See, page 1, lines 20-24 and page 2, lines 2-4. The amplification of this other RNA sequence can provide a positive control. See, page 1, lines 24-25 and page 2, lines 2. Three examples of target viral RNA are described on page 2, lines 6-32, namely one target from HIV-1 and two targets from HCMV. Primers and probes for amplifying and detecting each of these target sequences are described on page 2.

The '959 application notes that T-4 lymphocytes are primarily affected by HIV-1 which express the T-cell receptor. See, page 2, lines 33-35. A "'second primer' pair includes an oligonucleotide to amplify a sequence which is unique to the T-cell receptor." See, page 3, lines 1-3. Primers and a probe for amplifying and detecting the T-cell receptor are described at page 3, lines 7-11. The specification then describes "[A] 'third primer' pair is effective to amplify an RNA sequence present, preferably ubiquitously, in all of the cells of a peripheral blood sample … [P]referably … beta actin sequence." See, page 3, lines 12-16. Primers and a probe for amplifying and detecting a beta actin sequence are described at page 3, lines 18-22.

Example I of the '959 application describes the simultaneous amplification of an HIV-1 sequence and a T-cell receptor sequence using the HIV-1 primers disclosed on page 2 of the '959 application and the T-cell receptor primers disclosed on page 3 of the '959 application. The amplified HIV-1 sequence is detected using the HIV-1 probe disclosed on page 2 of the '959 application. The amplified T-cell receptor sequence is detected using the T-cell receptor probe disclosed on page 3 of the '959 application.

Example II of the '959 application describes the amplification of an HIV-1 sequence, a T-cell receptor sequence and a beta actin sequence. The HIV-1 sequence and T-cell receptor sequence are amplified and detected as described in Example I. The beta actin sequence is amplified using the beta actin primers disclosed on page 3 of the '959 application, and the amplified beta actin sequence is detected using the beta actin probe disclosed on page 3 of the '959 application.

It is clear from the description of the '959 application that the T-cell receptor and the beta actin gene are used as reference RNA sequences. It is well known to the skilled artisan that HIV-1 and HCMV are viruses, and the sequences amplified in accordance with the '959 application are viral RNA sequences. It is also well known to the skilled artisan that the T-cell receptor and beta actin are neither viruses nor viral genes.

According to the '959 application,

> A fourth primer … is provided by a reference RNA sequence which can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples."
>
> For HIV-1 such a reference RNA may be a "maxigene" formed by a multi-base pair insert into a unique site for example the unique KpnI site of the 3' ORF region. A preferred reference RNA includes a 22 base pair insert into the KpnI site of the HIV-1 3' ORF region of the pGEM92 clone described by Murakawa.

See, page 3, lines 23-31. The pGEM92 clone is a 1.1 kb BamHI restriction fragment of HIV-1 inserted into the pGEM2 vector. See, page 4, lines 3-10. The '959 application also discloses that the amplification

> product of this sequence 22 bases longer than the authentic HIV-sequence but still hybridizes to the 25 mer probe HIVC. It is therefore distinguishable by size from the authentic viral product.

See page 4, lines 11-14. The '959 application further discloses that

> The "maxigene" provides an internal control and an additional aid to quantitation.

See page 5, lines 1-2.

It is clear from this description in the '959 application that three potential reference sequences can be used and simultaneously amplified with the target viral RNA sequence. The

first reference sequence is a T-cell receptor sequence. The second reference sequence is a beta actin sequence. The third reference sequence is "fourth primer" or "maxigene." The plain language of the '959 application states that the "fourth primer" is a **reference RNA that can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples**. Applicants submit that the skilled artisan knows that the "fourth primer," i.e., reference RNA, comprises a viral RNA sequence. The '959 application then states that "[F]or HIV-1 such a reference RNA may be a 'maxigene.'" Thus, Applicants submit that the "fourth primer" equals a "reference RNA" equals the "maxigene." In view of the specific language found on page 3 of the '959 application, Applicants submit that the skilled artisan knows that the "fourth primer" is amplified by the same oligonucleotides as a target viral RNA sequence. Because the same oligonucleotides are used to amplify both the "fourth primer," i.e., "reference RNA," and the viral RNA sequence, it is apparent to the skilled artisan that the "fourth primer," i.e., "reference RNA," is a viral sequence. Since beta actin is not a viral sequence, Applicants submit that the "fourth primer," i.e., "reference RNA," cannot be beta actin, and the skilled artisan would know that the "fourth primer," i.e., "reference RNA," is a viral sequence and not beta actin. Consequently, Applicants submit that the Examiner's contention that the reference RNA on page 3 refers to a beta actin sequence is incorrect.

In addition, page 3 of the '959 application describes one example of a reference RNA for HIV-1. This reference RNA is a maxigene, which is formed by a multi-base insert into the 3' ORF of HIV-1. Furthermore, page 3, line 27 of the '959 application states "[F]or HIV-1 **such** a reference RNA may be a maxigene." (emphasis added) It is apparent to the skilled artisan that the term "**such**" refers to the reference RNA in the immediately preceding paragraph (i.e., line 25). This reference RNA is amplified by the same oligonucleotides as the viral RNA (lines 25-26). Thus, Applicants submit that it is apparent to the skilled artisan that the maxigene is a reference RNA which relates to a viral sequence and cannot refer to a beta actin sequence. Consequently, Applicants submit that the Examiner's contention that the reference RNA on page 3 refers to a beta actin sequence and not a reference maxigene is incorrect.

Furthermore, Applicants submit that Example III of the '959 application does not describe the use of a separate primer for maxigene amplification as asserted by the Examiner.

Example III describes the simultaneous amplification of the HIV-1 viral sequence, the T-cell receptor sequence and the "maxigene" sequence. That is, Example III states that Example I is repeated with the exception that the "maxigene primer" is included in the reaction mixture. As detailed above, Applicants submit that the "maxigene" is the "fourth primer," i.e., the "maxigene primer." No other primer is described in the '959 application. As described above, Example I discloses the simultaneous amplification of an HIV-1 sequence and a T-cell receptor sequence. Example I does not include the amplification of the beta-actin gene. Thus, the nucleic acids amplified in Example III include the HIV-1 sequence, the T-cell receptor sequence and the maxigene. The primers included in Example I are the primers for the HIV-1 sequence and the primers for the T-cell receptor sequence. Example I and thus Example III do not include primers for the beta-actin gene. Applicants submit that it is apparent to the skilled artisan that the only primers that are available in Example III for amplifying the nucleic acids present in the reaction mixture are those that are utilized in Example I, i.e., the only primers in Example III are the HIV-1 primers and the T-cell receptor primers. Since the maxigene, as disclosed on page 3 of the '959 application, comprises a multi-base pair insert into the 3' ORF of HIV-1, Applicants submit that it is apparent to the skilled artisan that the T-cell receptor primers will not amplify the maxigene sequence. Thus, Applicants submit that the skilled artisan knows from Example III that the HIV primers amplify both the HIV-1 viral sequence and the maxigene. Consequently, Applicants submit that Example III of the '959 application discloses that the same oligonucleotides are used to amplify both the target viral RNA sequence and the reference RNA sequence.

In view of the above analysis of the '959 application, Applicants submit that the maxigene is a reference RNA that is amplified and detected using the same oligonucleotides as the target viral RNA. Thus, Applicants submit that the present application is entitled to the priority date of the '959 application, i.e., 27 January 1988.

Rejection Over Wang et al.

In the Office Action dated 23 December 2008, the Examiner rejected claims 114, 115, 117, 118, 120, 122, 123, 125, 126, 128, 130, 131, 133, 134, 136, 138, 141, 142, 144, 146-151,

190-192, 194, 195, 197, 199-201, 203, 204, 206, 208-210, 212, 213, 215, 217-219, 221, 222, 224, 226-248 and 249-255 under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727). In this Office Action, the Examiner discussed the rejection first with respect to claims 114, 115, 117, 118, 120, 122, 123, 125, 126, 128, 130, 131, 133, 134, 136, 138, 141, 142, 144, 146-151, 190-192, 194, 195, 197, 199-201, 203, 204, 206, 208-210, 212, 213, 215, 217-219, 221, 222, 224 and 226-248 and second with respect to claims 249-255. Initially, Applicants note that claims 226-234 and 246-248 have been canceled. Since the remaining claims are directed to different subject matter, which the Examiner does not appear to have taken into consideration in maintaining the rejection of all of the previous claims, Applicants will separately discuss the rejection in the context of the claimed subject matter.

A. Amplification of Target Viral RNA Sequence and Reference RNA Sequence

As described above, claims 190-225 and 242-245 are directed to **a method for the amplification of target viral RNA and a reference RNA in a sample**. These claims are **not** directed to the quantitation of a target viral RNA in a sample. These claims include the steps of (a) adding a known quantity of a reference RNA sequence to a sample, (b) simultaneously subjecting the target viral RNA sequence and the reference RNA sequence to PCR amplification and (c) measuring the amounts of amplified selected viral RNA sequence and amplified reference sequence. The reference RNA sequence comprises a sequence present in the selected target viral RNA sequence and a sequence not present in the selected target viral RNA sequence. The reference RNA sequence and the target viral RNA sequence can be amplified by the same or different oligonucleotides. Following amplification, the amplified reference RNA sequence and amplified target viral RNA sequence are distinguishable by size or by probes. In step (b), the target viral RNA sequence if present in the sample and the reference RNA sequence are simultaneously amplified. It is evident from reading claims 190-225 and 242-245 that there is no step for

> calculating from the amplified target and standard segments produced in step (d) the amount of said target nucleic acid segment present in the sample before amplification.

This calculation step is required by the claims of Wang et al. See, for example, claim 1 of Wang et al. '727. Applicants also note that the preamble of claim 1 of Wang et al. '727 specifies that

the method is for quantifying a target nucleic acid in a sample. In order to quantify the target nucleic acid in a sample, it is necessary to calculate the amount of the target nucleic acid in the sample before amplification as set forth in step (f) of claim 1 of Wang et al. '727.

As amply illustrated above, the subject matter of claims 190-225 and 242-245 do not include a quantification step, i.e., a step of calculating the amount of target nucleic acid initially present in the sample. Because claims 190-225 and 242-245 of the present application do not include a step of calculating the amount of target nucleic acid in the sample before amplification, i.e., does not include a step for quantifying a target nucleic acid in a sample, Applicants submit that the claimed subject matter is neither the same nor substantially the same as the claimed subject matter of Wang et al. Thus, Applicants submit that Wang et al. does not anticipate claims 190-225 and 242-245 under 35 U.S.C. § 135(b).

Applicants note that Wang et al. is not prior art under any other section of Title 35 U.S.C. Specifically, Applicants note that Wang et al. was filed on 28 September 1989 claiming priority to an application filed on 21 August 1989. Thus, the earliest effective filing date for Wang et al. is 21 August 1989. As described above, Applicants are entitled to a priority of U.S. Serial No. 07/148,959 filed on 27 January 1988 which antedates the earliest effective filing date of Wang et al. In addition, Applicants submitted an unexecuted Declaration Under 37 CFR 1.131(a) on 29 November 2005 and submitted the executed Declaration Under 37 CFR 1.131(a) on 15 December 2005. This Declaration Under 37 CFR 1.131(a) swears behind the earliest effective filing date of Wang et al. Thus, Applicants submit that Wang et al. is not prior art under any other section of Title 35 U.S.C. (i.e., any section other than Section 135(b)), and therefore claims 190-225 and 242-245 are patentable over Wang et al. with respect to such sections of Title 35 U.S.C.

In view of the above remarks, Applicants submit that claims 190-225 and 242-245 are not anticipated by Wang et al. under 35 U.S.C. § 135(b) and are otherwise patentable over Wang et al. Withdrawal of this rejection is requested

B. Quantitation of Target Viral RNA Sequence

As described above, claims 249-255 are directed to **a method for the quantitation of target viral RNA in a sample**. Although these claims relate to a quantitation method,

Applicants submit that they are not claiming the same subject matter as Wang et al. because the claimed subject matter does not require the use of a shared primer pair.

Applicants do not generally disagree with the Examiner's analysis of Wang et al. However, Applicants submit that the claimed subject matter **does not require** the use of a shared primer pair, as was held by the BPAI in Interference No. 105,055. Since the claimed subject matter **does not require** the use of a shared primer pair, Wang et al. is not prior art under 35 U.S.C. § 135(b).

With respect to previously presented claims 249-255, Applicants submit that these claims are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727) in view of the Board's decisions Interference No. 105,055. First, Applicants submit that the Board's decision on Wang preliminary motion 1 (Paper 36 dated 5 November 2003 and titled Memorandum Opinion and Order) held that that Applicants are not claiming the same subject matter as claimed in the Wang et al. '727 patent. Applicants' basis for this contention is fully set forth in the Amendment filed 6 December 2007. As discussed in that Amendment the Board stated, "the dispositive question is whether 'a reference RNA which **can be amplified and detected by the same oligonucleotides** as used for authentic virus RNA samples' necessarily **requires** or results in the use of a shared primer pair." (Memorandum Opinion and Order, p. 20; emphasis added) The Board concluded that there was no disclosure in the specification that the preselected site should be chosen to avoid disrupting primer binding sites. (Memorandum Opinion and Order, pp. 21-22.) Thus, the Board concluded that although the Murakawa et al. earlier claims "encompass use of a shared primer pair, they **do not require** or necessarily result in use of a shared primer pair." (Memorandum Opinion and Order, p. 22; emphasis added.) In this regard, the Board stated "[I]t is possible to have a maxigene control sequence which can be amplified by different primers and detected by the same oligonucleotides used for the target sequence." (Memorandum Opinion and Order, p. 22.) The Board concluded that "binding to a shared primer pair is **neither excluded, required nor a necessary result**" in any of the Murakawa et al. earlier claims. (Memorandum Opinion and Order, p. 22; emphasis added.) Thus, the BPAI concluded that none of the earlier Murakawa claims are directed to the same or substantially the same invention as claimed in Wang et al. (Memorandum Opinion and Order, pp. 22-23.) These earlier claims

included claims that, when read in light of the specification, include a reference RNA that can be amplified and detected by the same oligonucleotides as the target RNA.

Thus, the Board specifically held that the language "can be amplified and detected by the same oligonucleotides," **did not require** or necessarily result in the use of a shared primer pair. Thus, Applicants submit that the Board has held that this language **does not require** the use of a shared primer pair. It is clear that the language of the claims "can be amplified by the same or different oligonucleotides" does not require use of a shared primer pair because different primers can be used by the plain language of the claims. If different primers can be used to amplify both the target viral RNA sequence and the reference RNA sequence, then it is clear that the use of a shared primer pair is not required, and it is clear that the method does not necessarily result in the use of a shared primer pair. Because the claims do not require the same primer pair, they are not barred by 35 U.S.C. § 135(b).

In addition, the term "can" in grammatical usage is used to merely express an ability. Ability means that it may happen, but there is no requirement that it must happen. Thus, Applicants submit that the term "can" as used in the claimed subject matter does not require or necessarily result in the use of a shared primer pair. Because the term "can" does not require the same primer pair, Applicants submit that the claims are not barred by 35 U.S.C. § 135(b).

Furthermore, Applicants note that the final step in claims 249-252 recite determining the relative amount of the target viral RNA sequence present in the sample before amplification. This step was one of the steps that the Board noted was different than the corresponding step in the Wang et al. '727 patent in concluding that Wang et al. '727 claim 1 was not obvious over Murakawa's proposed claim 50 in combination with the prior art. Specifically, the Board stated

> First, although the preamble of proposed claim 50 recites a "process for quantitation of a target viral RNA sequence, "proposed claim 50 does *not* contain the step of calculating the [absolute] amount of target RNA in the sample that is found in claim 1 of the Wang '727 patent" (Wang's opposition, Paper 44, p. 22). Instead, proposed claim 50 recites "determining the **relative quantification** of the target sequence" (step (v), emphasis added [in original]).

See, page 25 of Paper 47 dated 5 April 2004 and titled Decision on Preliminary Motion. If the determination of the "relative amount" as required by claims 249-252 is inherently the same as

calculating the absolute amount of target RNA as required by claim 1 of Wang et al. '727, then the Board could not have reached this conclusion. That is, the Board did not consider that the determining the relative amount was inherent because it would then have had to conclude that, at least on the basis of this step, the method of Wang et al. would have been obvious over the proposed Murakawa et al. claim. Because the Board did not so find, Applicants submit that the Examiner's contention concerning inherency with respect to step (v) of claim 249 is incorrect and contrary to the holding by the Board. For the above reasons, Applicants submit that claims 249-255 are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727).

Furthermore, as described above, Wang et al. is not prior art under any other section of Title 35 U.S.C. (i.e., any section other than Section 135(b)) with respect to claims 249-255, and therefore these claims are patentable over Wang et al. with respect to such sections of Title 35 U.S.C.

In view of the above remarks, Applicants submit that claims 249-255 are not anticipated by Wang et al. under 35 U.S.C. § 135(b) and are otherwise patentable over Wang et al. Withdrawal of this rejection is requested.

Rejection Over Wang et al. in view of Mullis et al.

In the Office Action dated 17 March 2008, the Examiner rejected claims 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 under 35 U.S.C. § 135(b) over Wang et al. in view of Mullis et al. (US 4,683,195). Applicants submit that the Examiner is in error in this rejection.

Specifically, Applicants submit that these claims are directed to a process for amplification of a target viral RNA and a reference RNA in a sample. As discussed above, these claims do not include a quantitation step as required by the claims of the Wang et al. Since the claims do not require a quantitation step as required by Wang et al., Applicants submit that the claimed subject matter is not the same and is not substantially the same as the claimed subject matter of Wang et al. for the reasons detailed above. Since the claimed subject matter of the present application is not the same and is not substantially the same as the Wang et al. claimed subject matter, Applicants submit that Wang et al. is not a bar to patentability under 35 U.S.C. § 135(b). Since Mulllis et al. does not disclose or suggest the claimed invention, Applicants

submit that Mullis et al. does not render the claimed subject matter obvious. Thus, Applicants submit that claims 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727) in view of Mullis et al.

Furthermore, as described above, Wang et al. is not prior art under any other section of Title 35 U.S.C. (i.e., any section other than Section 135(b)) with respect to claims 190-225 and 242-245, and therefore claims 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 are patentable over Wang et al. with respect to such sections of Title 35 U.S.C. in view of Mullis et al.

In view of the above remarks, Applicants submit that claims 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 are not rendered unpatentable under 35 U.S.C. § 135(b) over Wang et al. and Mullis et al., and are otherwise patentable over Wang et al. in view of Mullis et al. Withdrawal of this rejection is requested.

Concluding Comments

In view of the above amendments and remarks, it is submitted that the claims are fully supported by the instant application, entitled to a priority date of at least 27 January 1988 and are patentable over the prior art of record. Reconsideration of this application and early notice of allowance is requested. The Examiner is invited to telephone the undersigned if it will assist in expediting the prosecution and allowance of the instant application.

Respectfully submitted,

ROTHWELL, FIGG, ERNST & MANBECK, p.c.

By /Jeffrey L. Ihnen/

Jeffrey L. Ihnen
Registration No. 28,957
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
Telephone No.: (202) 783-6040
Facsimile No.: (202) 783-6031